MAIL STOP APPEAL BRIEF-PATENTS
PATENT
2503-1186

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	Appeal No.
Ezio BOMBARDELLI	Conf. 5416
Application No. 10/562,205	Group 1655
Filed May 15, 2006	Examiner Catheryne Chen

FORMULATIONS FOR THE TREATMENT
OF ARTHRITIS CONDITIONS

APPEAL BRIEF

MAY IT PLEASE YOUR HONORS: December 22, 2008

(i) Real Party in Interest

The real party in interest in this appeal is the Assignee, INDENA S.p.A. of Milan, Italy.

(ii) Related Appeals and Interferences

Neither the appellant, appellant's legal representative nor the assignee know of any other prior or pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(iii) Status of the Claims

Claims 1-5, 7 and 8 are pending, from whose final rejection this appeal is taken.

Claims 6 and 9 were cancelled.

(iv) Status of Amendments

There are no outstanding amendments. The claims have not been amended since the July 13, 2007 amendment. These claims were finally rejected by the Official Action mailed October 5, 2007, and, in response to the Pre-Appeal Brief Request for Review of April 1, 2008, subsequently rejected in the Official Action mailed July 18, 2008(the "Official Action"). The claims are as set forth in the Claims Appendix.

(v) Summary of Claimed Subject Matter

Claim 1 is the only independent claim.

Claim 1 is directed to formulations comprising:

- pure Saligenin or derivatives thereof or extracts containing them selected from saligenin-enriched *Salix rubra* extract; *(See, e.g., specification page 1, lines 19-21)*

- substantially pure boswellic acid or a semi-synthetic derivative thereof or a boswellic acid-enriched *Boswellia serrata* extract; *(See, e.g., specification page 1, lines 22-23)*

- procyanidins from *Vitis vinifera* or from *Camellia sinensis* or rhein or lipophilic derivatives thereof; *(See, e.g., specification page 1, lines 24-25)*

- N-acetyl-glucosamine; and *(See, e.g., specification page 2, line 1)*

- glucuronic acid or glucuronolactone. *(See, e.g., specification page 2, line 2)*

Claim 2 depends from claim 1, is directed to formulations as claimed in claim 1 comprising:

- *Salix rubra* extract containing 25% by weight of saligenin; *(See, e.g., specification page 2, line 7)*

- *Boswellia serrata* extract containing 20% of boswellic acid; *(See, e.g., specification page 2, line 8)*

- procyanidins from *Vitis vinifera* or from *Camellia sinensis* optionally complexed with phospholipids or rhein or lipophilic derivatives thereof; *(See, e.g., specification page 2, lines 9-10)*

- N-acetyl-glucosamine; and *(See, e.g., specification page 2, line 11)*

- glucuronic acid or glucuronolactone. *(See, e.g., specification page 2, line 12)*

Claim 3 depends from claim 1 and is directed to formulations as claimed in claim 1, wherein the *Salix rubra*

extract, the *Boswellia serrata* extract, procyanidins, N-acetyl-glucosamine, and glucuronic acid or glucuronolactone are present in 2:1:1:1:1 weight ratios, respectively. *(See, e.g., specification page 2, lines 13-15)*

Claim 4 depends from claim 1 and is directed to formulations as claimed in claim 2 containing 100 to 500 mg of 25% *Salix rubra* extract, 50 to 150 mg of procyanidins optionally in the form of complexes with phospholipids, 20 to 200 mg of *Boswellia serrata* extract, and 10 to 500 mg each of glucosamine, glucuronic acid or glucuronolactone. *(See, e.g., specification page 2, lines 16-19)*

(vi) Grounds of Rejection to be Reviewed on Appeal

Whether claims 1-4 were properly rejected as being unpatentable under 35 U.S.C. §103(a) over CHRUBASIK et al., Pain Digest, 1998 ("CHRUBASIK"), TAMEJA et al. U.S. 5,629,351 ("TAMEJA"), CHARTERS et al. U.S. 6,541,045 ("CHARTERS"), KEMPER http://www.mcp.edu/herbal/default.htm ("KEMPER"), GB 1015800("GB '800").

Whether claims 1-5, 7 and 8 were properly rejected as being unpatentable under 35 U.S.C. §103(a) over CHRUBASIK et al., Pain Digest, 1998 ("CHRUBASIK"), TAMEJA et al. U.S. 5,629,351 ("TAMEJA"), CHARTERS et al. U.S. 6,541,045 ("CHARTERS"), KEMPER

http://www.mcp.edu/herbal/default.htm ("KEMPER"), GB 1015800 ("GB '800"), further in view of CHEN et al. US 2002/0032171 A1 ("CHEN") and BELCH et al. The American Journal of Clinical Nutrition 2000 ("BELCH").

(vii) Arguments

The rejection of claims 1-4 as being unpatentable under 35 U.S.C. §103(a) over CHRUBASIK et al., Pain Digest, 1998 ("CHRUBASIK"), TANEJA et al. U.S. 5,629,351 ("TANEJA"), CHARTERS et al. U.S. 6,541,045 ("CHARTERS"), KEMPER http://www.mcp.edu/herbal/default.htm ("KEMPER"), GB 1015800("GB '800").

Claim 1

The combination fails to render obvious claim 1 for at least the following three reasons:

I. There would have been no reason to combine the documents.

The Examiner's position was that "it would be obvious to combine ingredients that have anti-inflammatory activities together because they are taught in the reference to have the same purpose." See, e.g., page 4, lines 6-15 of the Official Action.

However, the ingredients are not taught for the same purpose.

CHRUBASIK discloses the *Salix* species extract is a natural nonsteroidal anti-inflammatory drug that is used to treat rheumatic pain. See, e.g., page 231, Abstract and under both the "Summary" and "Oral Salix Preparations" headings.

KEMPER, however, which was offered for teaching oligomeric proanthocyanidin complexes (OPCs), fails to teach OPCs for the same purpose as the extracts of CHRUBASIK.

KEMPER discloses that OPCs are effective as anti-inflammatory ingredients with respect to allergic rhinitis, but not rheumatoid arthritis. Indeed, the OPCs are described as having no rheumatologic effect. See, page 6, "OPC: Potential Clinical Benefits."

Thus, one of ordinary skill in art would have had no reason to combine the ingredient of KEMPER with the composition of CHRUBASIK, or any of the other composition that treats inflammation associated rheumatoid arthritis, as the anti-inflammatory effect of OPCs is not a rheumatologic effect.

II. The combination does not teach the claimed composition.

Even if one were to combine the documents as proposed, the combination fails to disclose or suggest pure Saligenin, or derivatives thereof, or saligenin-enriched *Salix rubra* extract.

CHRUBASIK was offered for teaching the administration of a *Salix* species extract. However, the main component of this

extract is salicin, not saligenin. Indeed, CHRUBASIK discloses that salicin is converted to saligenin after administration. The flow chart of Figure 2 illustrates that salicin administered as the active component a pharmaceutical preparation is converted to saligenin in the gastrointestinal tract. See, e.g., at page 231 under the Studies on the "Biopharmaceutical Quality and Pharmacokinetics" heading and Figure 2 of page 233.

Thus, as CHRUBASIK fails to teach that for which it is offered, i.e., formulations comprising pure saligenin, or derivatives thereof, or saligenin-enriched *Salix rubra* extract, the proposed combination fails to teach the claimed composition.

III. The documents fail to recognize the synergistic effect achieved by the claimed composition.

The declaration filed July 13, 2007 demonstrated that the compounds have a synergistic effect when administered in combination for treating patients suffering from osteoarthritis of the knee. See, e.g., Tables 1-3 of the declaration included in the Appendix of this Brief. Appellant previously pointed out that Boswellia extract "senolee" of the declaration was a typographical error, and that Boswellia extract serrata was actually evaluated.

In order to prove that the results in the declaration demonstrate a synergistic effect, the pain data and the stiffness data from the declaration were analyzed according to the Bürgi

formula. The Bürgi formula is a universally accepted formula in pharmacology (See Acta Pharmacol Sin 2004 Feb; 25(2): 146-147, included in the appendix of this Brief and the response filed February 5, 2008). The results of the Bürgi formula analysis are discussed below:

q=observed value/expected value (the Bürgi formula) with a tolerance of ±0.15

where:
q=1 represents simple addition (i.e. additive effect)
q>1 represents synergism or potentiation
q<1 represents antagonism.

The expected value is the sum of the individual effects exerted by each compound, e.g., as administered to patient Groups 2-6. The individual effects are calculated as the difference between Day 0 and Day 14 values in Tables 1 and 2 below:

TABLE 1: Expected Value for Pain

Group	Effect
2	43.6 - 37.3= 6.3
3	43.7 - 37.3 = 4.6
4	43.5 - 41.1 = 2.4
5	45.1 - 42.8 = 2.3
6	44.9 - 44.5 = 0.4
Expected value for Pain	6.3 + 4.6 + 2.4 + 2.3 + 0.4 = **15**

TABLE 2: Expected Value for Stiffness

Group	Effect
2	42.4 - 44.1= -1.7
3	41.9 - 35.3 = 6.7
4	40.3 - 39.1 = 1.2
5	41.2 - 40.8 = 0.4
6	42.7 - 42.5 = 0.2
Expected value for Stiffness	-1.7 + 6.7 + 5.8 + 1.2 + 0.4 + 0.2 = **12.6**

The observed value is the effect of the combination of compounds, e.g., as administered to patient Group 7, which is calculated as the difference between the values from Day 0 and Day 14 in Tables 3 and 4:

TABLE 3: Observed Value for Pain (Group 7)
43.8 - 25.3 = **18.5**

TABLE 4: Observed Value for Stiffness (Group 7)
42.8 - 23.2 = **19.6**

Thus, parameter "q" based on Tables 1-4 above is:

q for Pain	**q for Stiffness**
18.5/15 = **1.23**	19.6/12.6 = **1.55**

As q is greater than 1, the compounds administered separately for Groups 2-6, i.e., Salix rubra extract, Boswellia serrata exact, Green tea extract, N-acetyl, glucosamine and Glucuronolactone, behave synergistically when administered together for Group 7, e.g., the claimed invention.

The standard deviation further suggests that the compounds exert a synergist effect. The difference in values between Day 0 and Day 14 in Groups 4, 5, and 6 are not statistically significant. That is, each single active compound fails to exert a significant effect on both pain and stiffness in the Day 0 to Day 14 period. The values for Group 7, however, are statistically significant for the same period.

Thus, the increased effect observed for Group 7 is attributed to the synergism of the five active compounds.

Therefore, reversal of the obviousness rejection of claim 1 is respectfully requested.

Claim 2

Further to the failings discussed relative to claim 1, the combination fails to teach a Salix rubra extract containing 25% by weight of saligenin.

The Examiner failed to address this feature.

CHRUBASIK was offered for teaching the administration of a *Salix* species extract. However, the main component of this extract is salicin, not saligenin. Indeed, CHRUBASIK illustrates this fact in the flow chart of Figure 2. Salicin is the active component that is administered, and saligenin is produced from metabolized salicin. See, e.g., at page 231 under the Studies on the "Biopharmaceutical Quality and Pharmacokinetics" heading and Figure 2 of page 233.

None of the other cited documents can remedy this shortcoming of CHRUBASIK for reference purposes.

Therefore, reversal of the obviousness rejection of claim 2 is also respectfully requested.

CLAIM 3

Further to the reasons given with respect to claim 1, the proposed combination cannot render obvious claim 3 for at least two reasons:

I. There is no suggestion of the claimed ratio.

The Examiner recognized that the documents fail to teach adding the ingredients in the claimed amount. However, the Examiner's position was that "the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize".

However, while CHRUBASIK, TAMEJA, CHARTERS, and GB '800 may each disclose effective ingredients for treating rheumatic pain or inflammation relating to rheumatoid arthritis, KEMPER discloses an ingredient having no rheumatologic effect.

Thus, one of ordinary skill in the art would have had no reason to "optimize" the amount of an ingredient identified as ineffective.

II. The cited documents fail to recognize the synergistic effect achieved by the claimed ratio.

The Examiner concluded that "absent demonstration of unexpected results from the claimed parameters, this optimization

of ingredient amount would have been obvious". See, e.g., the paragraph bridging pages 4 and 5 of the Official Action.

However, unexpected results from the claimed ratio were already made of record in the declaration filed July 13, 2007.

The results of the declaration were based on an exemplary composition of the claimed 2:1:1:1:1 ratio, i.e., *Salix rubra* extract, the *Boswellia serrata* extract, procyanidins, N-acetyl-glucosamine, and glucuronolactone, respectively. These results, for the reasons discussed above relative to claim 1, under reason III, show a synergistic effect that was not recognized by any of the cited documents.

Therefore, reversal of the obviousness rejection of claim 3 is also respectfully requested.

CLAIM 4

Further to the reasons discussed above with respect to claims 1 and 2, the proposed combination fails to render obvious claim 4 for at least two reasons:

I. The documents fail to disclose or suggest the claimed amounts.

The Examiner recognized that the documents fail to teach adding the ingredients in the claimed amounts. However, the Examiner's position was that "the amount of a specific

ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize".

While CHRUBASIK, TAMEJA, CHARTERS, and GB '800 suggest ingredients for treating rheumatic pain or inflammation relating to rheumatoid arthritis, KEMPER discloses an ingredient having no rheumatologic effect.

Thus, one of ordinary skill in the art would have had no reason to "optimize" the amount of an ingredient identified as ineffective for an intended use.

II. The cited documents fail to recognize the synergistic effect achieved by the claimed amounts

The Examiner concluded that "absent demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious". See, e.g., the paragraph bridging pages 4 and 5 of the Official Action.

However, unexpected results from the claimed amounts were already made of record in the declaration filed July 13, 2007.

The declaration showed results based on an exemplary composition that fell within the claimed ranges, e.g., 200 mg *Salix rubra* extract, 100 mg *Boswellia serrata* extract, 100 mg procyanidins, 100 mg N-acetyl-glucosamine, and 100 mg glucuronolactone. These results, for the reasons discussed above

relative to claim 1, under reason III, show a synergistic effect that was not recognized by any of the cited documents.

Therefore, reversal of the obviousness rejection of claim 4 is also respectfully requested.

The rejection of claims 1-5, 7 and 8 as being unpatentable under 35 U.S.C. §103(a) over CHRUBASIK et al., Pain Digest, 1998 ("CHRUBASIK"), TAMEJA et al. U.S. 5,629,351 ("TAMEJA"), CHARTERS et al. U.S. 6,541,045 ("CHARTERS"), KEMPER http://www.mcp.edu/herbal/default.htm ("KEMPER"), GB 1015800 ("GB '800"), further in view of CHEN et al. US 2002/0032171 A1 ("CHEN") and BELCH et al. The American Journal of Clinical Nutrition 2000 ("BELCH").

CHRUBASIK, TAMEJA, CHARTERS, KEMPER, and GB '800 are offered for the reasons discussed above under the first ground of rejection. This combination fails render obvious the features of claims 1-4 for the reasons discussed above with respect to the first ground of rejection.

CHEN are BELCH are solely offered for teaching the features of claim 5, which depends from claim 1, claim 7, which depends from claim 2, and claim 8, which depends from claim 3.

CHEN was offered for teaching triglycerides of Oenothera biennis oil (evening primrose oil) to improve the delivery of

therapeutic agents.

BELCH was offered for teaching evening primrose oil in supplements for rheumatic conditions.

However, neither CHEN nor BELCH teach (i) pure Saligenin or derivatives thereof or extracts containing them selected from saligenin-enriched *Salix rubra* extract, as recited in claim 1, such as 25% saligenin of claim 2, (ii) procyanidins, as recited in claim 1, for the same purposes as CHRUBASIK, TAMEJA, CHARTERS, and GB '800, and (iii) a synergistic effect resulting from the composition of claim 1 in the ratio of claim 3 or the amounts of claim 4.

Thus, regardless of the ability of CHEN and BELCH to teach that for which they are offered, these documents are not able to remedy the shortcomings of the combination of CHRUBASIK, TAMEJA, CHARTERS, KEMPER, and GB '800 for reference purposes.

Therefore, reversal of the obviousness rejection of dependent claims 1-5, 7, and 8 is respectfully requested.

Respectfully submitted,

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(viii) Claims Appendix

1. Formulations comprising:

- pure Saligenin or derivatives thereof or extracts containing them selected from saligenin-enriched *Salix rubra* extract;

- substantially pure boswellic acid or a semi-synthetic derivative thereof or a boswellic acid-enriched *Boswellia serrata* extract;

- procyanidins from *Vitis vinifera* or from *Camellia sinensis* or rhein or lipophilic derivatives thereof;

- N-acetyl-glucosamine; and

- glucuronic acid or glucuronolactone.

2. Formulations as claimed in claim 1 comprising:

- *Salix rubra* extract containing 25% by weight of saligenin;

- *Boswellia serrata* extract containing 20% of boswellic acid;

- procyanidins from *Vitis vinifera* or from *Camellia sinensis* optionally complexed with phospholipids or rhein or lipophilic derivatives thereof;

- N-acetyl-glucosamine; and

- glucuronic acid or glucuronolactone.

3. Formulations as claimed in claim 1 wherein the *Salix rubra* extract, the *Boswellia serrata* extract, procyanidins, N-acetyl-glucosamine, and glucuronic acid or glucuronolactone are present in 2:1:1:1:1 weight ratios, respectively.

4. Formulations as claimed in claim 2 containing 100 to 500 mg of 25% *Salix rubra* extract, 50 to 150 mg of procyanidins optionally in the form of complexes with phospholipids, 20 to 200 mg of *Boswellia serrata* extract, and 10 to 500 mg each of glucosamine, glucuronic acid or glucuronolactone.

5. Formulations as claimed in claim 1 in the form of capsules containing *Enothera biennis* oil as the carrier.

6. (cancelled)

7. Formulations as claimed in claim 2 in the form of capsules containing *Enothera biennis* oil as the carrier.

8. Formulations as claimed in claim 3 in the form of capsules containing *Enothera biennis* oil as the carrier.

9. (cancelled)

(ix) **Evidence Appendix**

- Declaration under 37 CFR 1.132, filed along with the Amendment of July 13, 2007.

- Acta Pharmacol Sin 2004 Feb; 25(2): 146-147, filed along with the Response of February 5, 2008.

(x) **Related Proceedings Appendix**

None.